

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION
(PCT Rule 61.2)

Date of mailing (day/month/year)
28 July 2000 (28.07.00)

To:

Assistant Commissioner for Patents
United States Patent and Trademark
Office
Box PCT
Washington, D.C.20231
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

International application No.
PCT/GB99/04355

Applicant's or agent's file reference
RW/SH/P32223

International filing date (day/month/year)
21 December 1999 (21.12.99)

Priority date (day/month/year)
21 December 1998 (21.12.98)

Applicant

MERRIFIED, David, Roy et al

1. The designated Office is hereby notified of its election made:

in the demand filed with the International Preliminary Examining Authority on:

24 June 2000 (24.06.00)

in a notice effecting later election filed with the International Bureau on:

2. The election was

was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer

Olivia RANAIVOJAONA

Telephone No.: (41-22) 338.83.38

TENT COOPERATION TREA

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NOTIFICATION OF THE RECORDING
OF A CHANGE(PCT Rule 92bis.1 and
Administrative Instructions, Section 422)

		From the INTERNATIONAL BUREAU												
		To:												
		WALKER, Ralph, Francis SmithKline Beecham Corporate Intellectual Property Two New Horizons Court Brentford Middlesex TW8 9EP ROYAUME-UNI												
Date of mailing (day/month/year)														
30 juillet 2001 (30.07.01)														
Applicant's or agent's file reference	IMPORTANT NOTIFICATION													
RW/SH/P32223														
International application No.	International filing date (day/month/year)													
PCT/GB99/04355	21 décembre 1999 (21.12.99)													
<p>1. The following indications appeared on record concerning:</p> <p><input checked="" type="checkbox"/> the applicant <input checked="" type="checkbox"/> the inventor <input type="checkbox"/> the agent <input type="checkbox"/> the common representative</p> <table border="1"> <tr> <td rowspan="4">Name and Address WARR, John, Peter GlaxoSmithKline Pharmaceuticals New Frontiers Science Park South Third Avenue Harlow Essex CM19 5AW United Kingdom</td> <td>State of Nationality</td> <td>State of Residence</td> </tr> <tr> <td>GB</td> <td>GB</td> </tr> <tr> <td colspan="2">Telephone No.</td> </tr> <tr> <td colspan="2">Facsimile No.</td> </tr> <tr> <td colspan="2">Teleprinter No.</td> </tr> </table>				Name and Address WARR, John, Peter GlaxoSmithKline Pharmaceuticals New Frontiers Science Park South Third Avenue Harlow Essex CM19 5AW United Kingdom	State of Nationality	State of Residence	GB	GB	Telephone No.		Facsimile No.		Teleprinter No.	
Name and Address WARR, John, Peter GlaxoSmithKline Pharmaceuticals New Frontiers Science Park South Third Avenue Harlow Essex CM19 5AW United Kingdom	State of Nationality	State of Residence												
	GB	GB												
	Telephone No.													
	Facsimile No.													
Teleprinter No.														
<p>2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:</p> <p><input checked="" type="checkbox"/> the person <input checked="" type="checkbox"/> the name <input checked="" type="checkbox"/> the address <input checked="" type="checkbox"/> the nationality <input checked="" type="checkbox"/> the residence</p> <table border="1"> <tr> <td rowspan="4">Name and Address WARR, John, Peter GlaxoSmithKline Pharmaceuticals New Frontiers Science Park South Third Avenue Harlow Essex CM19 5AW United Kingdom</td> <td>State of Nationality</td> <td>State of Residence</td> </tr> <tr> <td>GB</td> <td>GB</td> </tr> <tr> <td colspan="2">Telephone No.</td> </tr> <tr> <td colspan="2">Facsimile No.</td> </tr> <tr> <td colspan="2">Teleprinter No.</td> </tr> </table>				Name and Address WARR, John, Peter GlaxoSmithKline Pharmaceuticals New Frontiers Science Park South Third Avenue Harlow Essex CM19 5AW United Kingdom	State of Nationality	State of Residence	GB	GB	Telephone No.		Facsimile No.		Teleprinter No.	
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	GB	GB												
	Telephone No.													
	Facsimile No.													
Teleprinter No.														
<p>3. Further observations, if necessary: Additional applicant and inventor for US only.</p>														
<p>4. A copy of this notification has been sent to:</p> <table> <tr> <td><input checked="" type="checkbox"/> the receiving Office</td> <td><input type="checkbox"/> the designated Offices concerned</td> </tr> <tr> <td><input type="checkbox"/> the International Searching Authority</td> <td><input checked="" type="checkbox"/> the elected Offices concerned</td> </tr> <tr> <td><input type="checkbox"/> the International Preliminary Examining Authority</td> <td><input type="checkbox"/> other:</td> </tr> </table>				<input checked="" type="checkbox"/> the receiving Office	<input type="checkbox"/> the designated Offices concerned	<input type="checkbox"/> the International Searching Authority	<input checked="" type="checkbox"/> the elected Offices concerned	<input type="checkbox"/> the International Preliminary Examining Authority	<input type="checkbox"/> other:					
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<input type="checkbox"/> the International Preliminary Examining Authority	<input type="checkbox"/> other:													
The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No.: (41-22) 740.14.35	Authorized officer I. Britel Telephone No.: (41-22) 338.83.38													

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REC'D 23 MAR 2001
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INTERNATIONAL PRELIMINARY EXAMINATION REPORT (PCT Article 36 and Rule 70)

Applicant's or agent's file reference RFW/P32223	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/GB99/04355	International filing date (<i>day/month/year</i>) 21/12/1999	Priority date (<i>day/month/year</i>) 21/12/1998
International Patent Classification (IPC) or national classification and IPC B01J2/04		
Applicant SMITHKLINE BEECHAM PLC et al.		
<p>1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of 5 sheets, including this cover sheet.</p> <p><input checked="" type="checkbox"/> This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).</p> <p>These annexes consist of a total of 6 sheets.</p>		
<p>3. This report contains indications relating to the following items:</p> <ul style="list-style-type: none"> I <input checked="" type="checkbox"/> Basis of the report II <input type="checkbox"/> Priority III <input type="checkbox"/> Non-establishment of opinion with regard to novelty, inventive step and industrial applicability IV <input type="checkbox"/> Lack of unity of invention V <input checked="" type="checkbox"/> Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement VI <input type="checkbox"/> Certain documents cited VII <input type="checkbox"/> Certain defects in the international application VIII <input checked="" type="checkbox"/> Certain observations on the international application 		

Date of submission of the demand 24/06/2000	Date of completion of this report 21.03.2001
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Rumbo, A Telephone No. +49 89 2399 8407



**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/GB99/04355

I. Basis of the report

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments (Rules 70.16 and 70.17).)*):

Description, pages:

1-23 as originally filed

Claims, No.:

1-40 as received on 26/01/2001 with letter of 26/01/2001

Drawings, sheets:

1,2 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- the language of publication of the international application (under Rule 48.3(b)).
- the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- contained in the international application in written form.
- filed together with the international application in computer readable form.
- furnished subsequently to this Authority in written form.
- furnished subsequently to this Authority in computer readable form.
- The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- the description, pages:
- the claims, Nos.:

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/GB99/04355

the drawings, sheets:

5. This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims 1-27, 29-40
	No:	Claims 28
Inventive step (IS)	Yes:	Claims
	No:	Claims 1-40
Industrial applicability (IA)	Yes:	Claims 1-40
	No:	Claims

2. Citations and explanations
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/GB99/04355

SECTION VIII (CLARITY)

1. The claimed subject-matter does not meet the requirements of Article 6 PCT. The presence of two independent process claims (#1 and #19) each of them containing technical features completely different from those contained in the wording of the other, **does not allow third parties to know which of them are essential for the invention to be performed and which other merely constitute optional technical features.**

In fact, the features:

- a) stream comprising additive in a fluid carrier vehicle
- b) stream comprising material and compressible fluid antisolvent
- c) addition of stream a) into stream b)

present in the wording of independent claim 19 are not disclosed in claim 1.

SECTION V (NOVELTY AND INVENTIVE STEP)

2. The claimed subject-matter does not meet the requirements of Article 33(2) PCT.

There are disclosures of the prior art which contain all the technical features of the products at present in the wording of claim 28. Taking into account that a product is not made novel merely by the fact that it has been obtained by means of a new process, the products disclosed at examples 3 to 5 of D1= WO-A-9600610 are prejudicial for the novelty of present claim 28.

3. The novelty of the claimed process and devices has been established by introducing the terms "**a region in direct downstream communication with the orifice** and which is provided with means to cause the pressure and temperature conditions therein to be such that the compressible fluid antisolvent substance in the downstream region is in a gaseous state"

In fact the apparatus disclosed in figure 1, 2A, 2B, and 3 of D1 is **not in direct downstream communication** with the orifice to cause antisolvent to go into gaseous state, but **it is in an indirect downstream communication** (see conduit 17, vessel 9) to a section meeting such conditions.

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/GB99/04355

It is evident that no difference can be obtained merely as a consequence of a direct communication in comparison with an indirect one as regards the solution of a technical problem by the claimed subject-matter in view of D1.

In any case, the principle of rendering the solvent gaseous in order to precipitate the solved substances is well known in the state of the art (see reference to RESS in D1, page 2, lines 10-15 and to GAS at page 2, lines 23 to 28) and the skilled person can use it in an obvious way without implying any inventive step.

At present time nowhere in the application as filed it is disclosed that a technical problem can be solved by technical means been different from those well known for the skilled person.

The claimed subject-matter (claims 1 to 40) does not meet, therefore, the requirements of Article 33(3) PCT.

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Claims: PCT amended January 2001

1. A process for the production of particles of a material wherein:
a stream of a dispersion of the material in a solvent and a stream of a compressible fluid antisolvent substance are brought into contact with each other so that the streams combine to form a mixture under conditions such that the substance is in compressible fluid antisolvent state,
the mixture is then caused to flow along a conduit extending downstream from the region where the streams come into contact, toward an orifice which opens from the conduit directly into a downstream region so that the mixture flows through the orifice into the downstream region,
the pressure and temperature of the mixture in the conduit being such that the compressible fluid antisolvent substance remains in a compressed state over at least part of the length of the conduit,
the pressure and temperature in the downstream region being such that the compressible fluid antisolvent is present therein in a gaseous state and the material separates from the mixture in a particulate state as a consequence of the conversion of the compressible fluid antisolvent into a gas.
- 20 2. A process according to claim 1 characterised in that the compressible fluid antisolvent substance is a substance in supercritical fluid state.
3. A process according to claim 1 or 2 characterised in that in the downstream region the pressure is 1-20 bar, and the temperature is 0-50°C.
- 25 4. A process according to claim 3 characterised in that in the downstream region the pressure is around atmospheric.
5. A process according to any one of claims 1 to 4 characterised in that the compressible fluid antisolvent substance comprises carbon dioxide.

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6. A process according to claim 5 characterised in that the carbon dioxide is in a supercritical fluid state.
7. A process according to any preceding claim characterised in that the solvent is an organic solvent selected from C₁₋₅ alkyl C₁₋₅ alkanoate esters, C₁₋₅ alcohols, and di- C₁₋₅ alkyl ketones, halogenated organic solvents, water, and mixtures thereof.
8. A process according to any preceding claim characterised in that the solvent is saturated or near saturated with the material.
9. A process according to any one of claims 2 to 8 characterised in that a supercritical fluid substance : dispersion ratio of 50 or less : 1 is used.
10. A process according to any one of the preceding claims characterised in that one or more additives and/or modifiers are introduced into the mixture of the material, the solvent and the compressible fluid antisolvent substance.
11. A process according to claim 10 characterised in that one or more of the additives is a solid, and is introduced as a dispersion in a carrier vehicle.
12. A process according to claim 10 or 11 characterised in that the additive and/or modifier is introduced into the input stream of dispersion of the material and/or the compressible fluid antisolvent substance.
13. A process according to claim 10 or 11 characterised in that the additive and/or modifier is mixed with one or both of the input streams before this is inputted.
14. A process according to claim 10 or 11 characterised in that the one or more additives and/or modifier is separately introduced into the region where the streams mix
15. A process according to claim 10 or 11 characterised in that the one or more additives and/or modifier is introduced into the mixture of the dispersion and the compressible fluid

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antisolvent substance at the region where the streams of dispersion and compressible fluid antisolvent substance contact each other.

16. A process according to claim 10 or 11 characterised in that the one or more additives
5 and/or modifier is introduced into the mixture of the dispersion and the compressible fluid antisolvent substance in the conduit between the region where the solution and the compressible fluid antisolvent substance meet and the orifice.

17. A process according to claim 10 or 11 characterised in that the one or more additive is
10 introduced into the mixture at a point downstream of the part of the process where the compressible fluid antisolvent substance decompresses.

18. A process according to any one of claims 10 to 17 characterised in that the one or
more additive is an excipient material.
15

19. A process for forming a co-formulation of a material and an additive in which a mixture of a material and an additive is produced by introducing the additive, in a fluid carrier vehicle, into a stream comprising the material and a compressible fluid antisolvent substance, and then causing the mixed stream to flow into a downstream region where the
20 compressible fluid antisolvent substance decompresses.

20. A process according to any preceding claim characterised in that the pressure and temperature of the mixture in the conduit are maintained by means of the dimensions of the conduit being such as to generate a back pressure in part or all of the conduit between the
25 region where the streams meet and the orifice.

21. A process according to any preceding claim characterised in that a pressurised gas is introduced into the flow of mixture between the region where the streams meet and the orifice.
30

22. A process according to any preceding claim characterised in that the flow of the mixture is restricted in the conduit, between an upstream high pressure zone and a

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downstream lower pressure zone, and a flow control fluid is introduced into the conduit upstream of the restriction, the pressure of the flow control fluid being equal to or greater than the pressure of the flowing fluid upstream of the restriction.

5 23. A process according to any preceding claim characterised in that a heat carrier fluid may be introduced into the mixture flowing along the conduit.

24. A process according to any one of the preceding claims, characterised by drying means in the downstream region.

10 25. A process according to claim 24, characterised in that materials carried in an aqueous vehicle are dried by the drying means.

15 26. A process according to claim 24 or 25 characterised in that the drying means entrains the particles in the downstream region in a stream of gas.

27. A process according to any preceding claim characterised in that particles which are formed in the process are collected.

20 28. A particulate product material made using a process as claimed in any preceding claim.

25 29. An apparatus suitable for performing a process as claimed in claim 1 comprising: means (11, 13, 21, 23, 31, 33) for bringing a stream of a dispersion of the material in a solvent and a stream of a compressible fluid antisolvent substance into contact with each other such that the streams combine to form a mixture under conditions such that the substance is in a compressible fluid antisolvent state,

a conduit (17, 27, 37) extending downstream from the region where the streams come into contact toward an orifice (18, 28, 38), along which the mixture can flow,

30 means to cause the pressure and temperature of the mixture in the conduit (17, 27, 37) to be such that the substance remains in a compressible fluid antisolvent state along at least part of the conduit (17, 27, 37),

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a region (19, 29, 39) in direct downstream communication with the orifice and which is provided with means to cause the pressure and temperature conditions therein to be such that the compressible fluid antisolvent substance in the downstream region is in a gaseous state.

5

30. An apparatus according to claim 29, characterised in that: the means to cause the pressure and temperature of the mixture in the conduit (17, 27, 37) to be such that the substance remains in a compressible antisolvent state along at least part of the conduit (17, 27, 37) are means to cause the substance to remain in a supercritical fluid state.

10

31. An apparatus according to claim 29 or 30 characterised by a "T" or "Y" tube system (15, 25) to bring the dispersion of the material and the compressible fluid antisolvent substance into contact with each other by flowing them along respective limbs of the "T" or "Y" and to provide the conduit (17, 27) as the stem of the "T" or "Y".

15

32. An apparatus according to claim 31 characterised in that the orifice (18, 28, 38) is provided at the end of the limb remote from the junction (15, 25) of the limbs.

20

33. An apparatus according to any one of claims 29 to 32 characterised by introduction (319, 325) means for the introduction of one or more additive and/or modifier.

25

34. An apparatus according to claim 33 characterised in that the introduction means comprises an "X" tube arrangement (31, 33, 325, 37), the respective streams of dispersion of material and compressible fluid antisolvent substance being introduced via two respective limbs (31, 33) of the "X" tube arrangement, the additive being introduced into the flow via a third limb (325) of the "X" tube, and the fourth limb (37) of the "X" comprising the conduit.

30

35. An apparatus according to claim 34 characterised in that the introduction means comprises a further "T" or "Y" tube arrangement (37, 319), located downstream of the point where the dispersion and compressible fluid antisolvent substance meet.

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36. An apparatus according to any one of claims 29 to 35 characterised in that the means to cause the pressure and temperature of the mixture in the conduit (17, 27, 37) to be such that the substance remains in a compressible fluid antisolvent state comprise the conduit (17, 27, 37) having dimensions such as to generate a back pressure in part or all of the conduit between the region where the streams meet and the orifice (18, 28, 38).

5

37. An apparatus according to any one of claims 29 to 36 characterised by pressurised gas introduction means (214) to introduce a pressurised gas directly into the conduit (27).

10 38. An apparatus according to any one of claims 29 to 37 characterised by a drying means to dry particles which are formed.

39. An apparatus according to claim 38 characterised in that the drying means introduces a stream of heated air around the orifice.

15

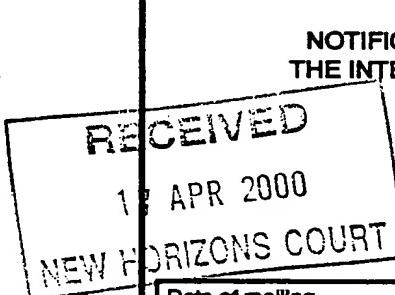
40. An apparatus according to any one of claims 29 to 39 provided with a downstream region for collection of the particles.

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

To:
SmithKline Beecham p.l.c.
Corporate Intellectual Property
Attn. WALKER, RALPH FRANCIS
Two New Horizons Court
Brentford
Middlesex TW8 9EP
UNITED KINGDOM



**NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL SEARCH REPORT
OR THE DECLARATION**

(PCT Rule 44.1)

Applicant's or agent's file reference RW/SH/P32223	Date of mailing (day/month/year) 14/04/2000
International application No. PCT/GB 99/04355	FOR FURTHER ACTION See paragraphs 1 and 4 below International filing date (day/month/year) 21/12/1999
Applicant SMITHKLINE BEECHAM PLC et al.	

1. The applicant is hereby notified that the International Search Report has been established and is transmitted herewith.

Filing of amendments and statement under Article 18:

The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the International Search Report; however, for more details, see the notes on the accompanying sheet.

Where? Directly to the International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland
Facsimile No.: (41-22) 740.14.35

For more detailed instructions, see the notes on the accompanying sheet.

2. The applicant is hereby notified that no International Search Report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

3. With regard to the protest against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. Further action(s): The applicant is reminded of the following:

Shortly after 18 months from the priority date, the International application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the International application, or of the priority claim, must reach the International Bureau as provided in Rules 90bis.1 and 90bis.3, respectively, before the completion of the technical preparations for International publication.

Within 19 months from the priority date, a demand for International preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later).

Within 20 months from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected in the demand or in a later election within 19 months from the priority date or could not be elected because they are not bound by Chapter II.

Name and mailing address of the International Searching Authority  European Patent Office, P.B. 5818 Patenttaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer Chantal Meyer
---	--

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the PCT Applicant's Guide, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only.

What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When?

Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How?

Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

NOTES TO FORM PCT/ISA/220 (continued)

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped), whether

- (i) the claim is unchanged;
- (ii) the claim is cancelled;
- (iii) the claim is new;
- (iv) the claim replaces one or more claims as filed;
- (v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."
2. [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11."
3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."
4. [Where various kinds of amendments are made]:
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

It must be in the language in which the International application is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

Consequence if a demand for International preliminary examination has already been filed

If, at the time of filing any amendments under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the same time of filing the amendments with the International Bureau, also file a copy of such amendments with the International Preliminary Examining Authority (see Rule 52.2(a), first sentence).

Consequence with regard to translation of the International application for entry into the national phase

The applicant's attention is drawn to the fact that, where upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see Volume II of the PCT Applicant's Guide.

PATENT COOPERATION TREATY

RECEIVED

- 6 AUG 2001 PCT
NEW HORIZONS COURT

NOTIFICATION OF THE RECORDING
OF A CHANGE(PCT Rule 92bis.1 and
Administrative Instructions, Section 422)Date of mailing (day/month/year)
30 July 2001 (30.07.01)

From the INTERNATIONAL BUREAU

To:

WALKER, Ralph, Francis
SmithKline Beecham
Corporate Intellectual Property
Two New Horizons Court
Brentford
Middlesex TW8 9EP
ROYAUME-UNI

Applicant's or agent's file reference
RW/SH/P32223

IMPORTANT NOTIFICATION

International application No.
PCT/GB99/04355International filing date (day/month/year)
21 December 1999 (21.12.99)

1. The following indications appeared on record concerning:

 the applicant the inventor the agent the common representative

Name and Address

WARR, John, Peter
GlaxoSmithKline Pharmaceuticals
New Frontiers Science Park South
Third Avenue
Harlow
Essex CM19 5AW
United Kingdom

State of Nationality

GB

State of Residence

GB

Telephone No.

Facsimile No.

Teleprinter No.

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

 the person the name the address the nationality the residence

Name and Address

WARR, John, Peter
GlaxoSmithKline Pharmaceuticals
New Frontiers Science Park South
Third Avenue
Harlow
Essex CM19 5AW
United Kingdom

State of Nationality

GB

State of Residence

GB

Telephone No.

Facsimile No.

Teleprinter No.

3. Further observations, if necessary:

Additional applicant and inventor for US only.

4. A copy of this notification has been sent to:

<input checked="" type="checkbox"/> the receiving Office	<input type="checkbox"/> the designated Offices concerned
<input type="checkbox"/> the International Searching Authority	<input checked="" type="checkbox"/> the elected Offices concerned
<input type="checkbox"/> the International Preliminary Examining Authority	<input type="checkbox"/> other:

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Authorized officer

J. Britel

Facsimile No.: (41-22) 740.14.35

Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREATY

PCT

NOTIFICATION OF THE RECORDING
OF A CHANGE(PCT Rule 92bis.1 and
Administrative Instructions, Section 422)Date of mailing (day/month/year)
30 July 2001 (30.07.01)

From the INTERNATIONAL BUREAU

To:

WALKER, Ralph, Francis
 SmithKline Beecham
 Corporate Intellectual Property
 Two New Horizons Court
 Brentford TW8 9EP
 Middlesex ROYAUME-UNI - 6 AUG 2001
GlaxoSmithKline
Corporate I.P.

Applicant's or agent's file reference
RW/SH/P32223~~Received 2001-08-06~~
IMPORTANT NOTIFICATIONInternational application No.
PCT/GB99/04355International filing date (day/month/year)
21 December 1999 (21.12.99)

1. The following indications appeared on record concerning:

 the applicant the inventor the agent the common representative

Name and Address

AVONTUUR, Petrus, Paulus, Cornelis
 GlaxoSmithKline Pharmaceuticals
 New Frontiers Science Park South
 Third Avenue
 Harlow
 Essex CM19 5AW
 United Kingdom

State of Nationality

GB

State of Residence

GB

Telephone No.

Facsimile No.

Teleprinter No.

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

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State of Nationality

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State of Residence

GB

Telephone No.

Facsimile No.

Teleprinter No.

3. Further observations, if necessary:

Additional applicant and inventor for US only.

4. A copy of this notification has been sent to:

 the receiving Office
 the International Searching Authority
 the International Preliminary Examining Authority

 the designated Offices concerned
 the elected Offices concerned
 other:

The International Bureau of WIPO
 34, chemin des Colombettes
 1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer

I. Britel

Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREATY

PCT

From the INTERNATIONAL BUREAU

To:

WALKER, Ralph, Francis
 SmithKline Beecham
 Corporate Intellectual Property
 Two New Horizons Court
 Brentford
 Middlesex TW8 9EP
 ROYAUME-UNI

IMPORTANT NOTIFICATION
6 AUG 2001

Date of mailing (day/month/year)
30 July 2001 (30.07.01)
Applicant's or agent's file reference
RW/SH/P32223
International application No.
PCT/GB99/04355

International filing date (day/month/year)

21 December 1999 (21.12.99)

1. The following indications appeared on record concerning:

the applicant the inventor the agent the common representative

Name and Address	State of Nationality	State of Residence
SOUTER, Andrew, Robert GlaxoSmithKline Pharmaceuticals New Frontiers Science Park South Third Avenue Harlow Essex CM19 5AW United Kingdom	GB	GB
	Telephone No.	
	Faximile No.	
	Teleprinter No.	

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

the person the name the address the nationality the residence

Name and Address	State of Nationality	State of Residence
SOUTER, Andrew, Robert GlaxoSmithKline Pharmaceuticals New Frontiers Science Park South Third Avenue Harlow Essex CM19 5AW United Kingdom	GB	GB
	Telephone No.	
	Faximile No.	
	Teleprinter No.	

3. Further observations, if necessary:

Additional applicant and inventor for US only.

4. A copy of this notification has been sent to:

<input checked="" type="checkbox"/> the receiving Office	<input type="checkbox"/> the designated Offices concerned
<input type="checkbox"/> the International Searching Authority	<input checked="" type="checkbox"/> the elected Offices concerned
<input type="checkbox"/> the International Preliminary Examining Authority	<input type="checkbox"/> other:

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer
Facsimile No.: (41-22) 740.14.36	I. Britel
	Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference RW/SH/P32223	FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. PCT/GB 99/04355	International filing date (day/month/year) 21/12/1999	(Earliest) Priority Date (day/month/year) 21/12/1998
Applicant SMITHKLINE BEECHAM PLC et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 4 sheets.

It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

- a. With regard to the language, the International search was carried out on the basis of the International application in the language in which it was filed, unless otherwise indicated under this item.
 - the International search was carried out on the basis of a translation of the International application furnished to this Authority (Rule 23.1(b)).
- b. With regard to any nucleotide and/or amino acid sequence disclosed in the International application, the International search was carried out on the basis of the sequence listing :
 - contained in the International application in written form.
 - filed together with the International application in computer readable form.
 - furnished subsequently to this Authority in written form.
 - furnished subsequently to this Authority in computer readable form.
 - the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the International application as filed has been furnished.
 - the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. Certain claims were found unsearchable (See Box I).

3. Unity of invention is lacking (see Box II).

4. With regard to the title,

- the text is approved as submitted by the applicant.
- the text has been established by this Authority to read as follows:

PROCESS AND APPARATUS FOR PRODUCING PARTICLES USING A SUPERCRITICAL FLUID

5. With regard to the abstract,

- the text is approved as submitted by the applicant.
- the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this International search report, submit comments to this Authority.

6. The figure of the drawings to be published with the abstract is Figure No.

- as suggested by the applicant.
- because the applicant failed to suggest a figure.
- because this figure better characterizes the invention.

1

None of the figures.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/GB 99/04355

Box III TEXT OF THE ABSTRACT (Continuation of Item 5 of the first sheet)

LINE 4 AFTER "CONDUIT" INSERT "(17)"
LINE 4 AFTER "ORIFICE" INSERT "(18)"

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 99/04355

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 B01J2/04 A61K9/16

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 B01J A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>WO 96 00610 A (HANNA MAZEN ;UNIV BRADFORD (GB); YORK PETER (GB)) 11 January 1996 (1996-01-11)</p> <p>page 1, line 4 - line 8 page 6, line 19 -page 9, line 1 page 12, line 16 -page 13, line 15 page 13, line 27 -page 14, line 31 page 19, line 29 -page 21, line 20 page 21, line 32 -page 22, line 21 page 27, line 30 -page 29, line 3 page 30, line 12 - line 29; claims 1-20; figures 1,2A,2B,4A</p> <p style="text-align: center;">-/-</p>	<p>1,6-15, 17-19, 23-32, 37,39-41</p>

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the International filing date
- "L" document which may throw doubts on priority, claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the International filing date but later than the priority date claimed

- "T" later document published after the International filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the International search

7 April 2000

Date of mailing of the International search report

14/04/2000

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3018

Authorized officer

Cubas Alcaraz, J

INTERNATIONAL SEARCH REPORT

National Application No

PCT/GB 99/04355

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 97 31691 A (UNIV KANSAS ;SUBRAMANIAM BALA (US); SAID SAID (US); RAJEWSKI ROGER) 4 September 1997 (1997-09-04) cited in the application claims 1-57; figures 1,2	1-41

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No.

B 99/04355

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO 9600610	A 11-01-1996	AT 174531	T	15-01-1999
		AU 688526	B	12-03-1998
		AU 2800395	A	25-01-1996
		CA 2192811	A	11-01-1996
		DE 69506707	D	28-01-1999
		DE 69506707	T	01-07-1999
		EP 0767702	A	16-04-1997
		ES 2128743	T	16-05-1999
		GR 3029531	T	30-06-1999
		JP 10502016	T	24-02-1998
		ZA 9505437	A	16-02-1996
WO 9731691	A 04-09-1997	US 5874029	A	23-02-1999
		US 5833891	A	10-11-1998
		AU 709384	B	26-08-1999
		AU 2193697	A	16-09-1997
		CA 2247900	A	04-09-1997
		EP 0885038	A	23-12-1998